REMARKS

The amendments at page 2, lines 25 and 29, are to correct obvious typographical errors.

The amendments at page 5, lines 17-18, are to correct obvious typographical errors.

The amendment at page 9, line 6, inserting "(middle panel)" and deleting the superfluous "PTTG" is to correct an obvious typographical error and is supported by Figure 5 as originally filed.

The amendment at page 9, line 10, inserting "(middle panel)" is to correct a typographical error and is supported by Figure 6 as originally filed.

The amendment at page 9, line 13, inserting the word "anti-" in front of "CD3" is to correct a typographical error and is supported, e.g., at page 9, lines 13 and 17.

The amendment at page 9, line 14, deleting "PTTG" and inserting "(middle panel)" is to correct a typographical error and is supported by Figure 7 as originally filed.

The amendment at page 9, line 17, inserting the word "anti-" in front of "CD3" is to correct a typographical error and is supported, e.g., at page 9, lines 13 and 17.

The amendment at page 9, line 18, deleting "PTTG" and inserting "(middle panel)" is to correct a typographical error and is supported by Figure 8 as originally filed.

The amendment at page 9, line 21, inserting "(middle panel)" is to correct a typographical error and is supported by Figure 9 as originally filed.

The amendment at page 9, line 23, replacing "ml" with "mL" is to correct an obvious typographical error.

The amendment at page 9, line 25, inserting "(middle panel)" is to correct a typographical error and is supported by Figure 10 as originally filed.

The amendment at page 10, line 9, inserting the sentence "*PTTG* mRNA was measured with northern blotting (middle panel) and percentage of cells in S phase was determined by FACS." is supported in the specification as originally filed, e.g., at page 9, lines 23-25 and page 82, line 28 through page 84 line 14.

The amendment at page 98, lines 14 and 16, correcting the spelling of "GFR Matrigel" is to correct an obvious typographical error, and additional support is found in the specification as originally filed, e.g., at page 12, line 10.

The insertion of "(Figure 23B)," at page 99, line 11, is to correct a typographical error, and is supported in Figure 23B, as originally filed.

The insertion of Figure 19 is to correct an inadvertent omission. Figure 19 was submitted with U.S. Serial No. 09/777,422, filed February 5, 2001, the specification of which was incorporated by reference into the above-captioned application, as stated in the specification as originally filed, at page 7, line 26 through page 8, line 1. Therefore, Figure 19 was, in fact, deposited in the USPTO at the time the above-captioned application was filed. Further, recitations of "Figure 19" occur in the specification as originally filed, for example, at page 11, lines 9-14; and at page 97, line 7. Applicant has submitted herewith a petition and the requisite fee concerning inclusion of Figure 19 into the above-captioned application.

Applicant believes that no new matter is introduced by any amendments made herein.

In view of the above amendments and remarks, it is submitted that this application is now ready for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (213) 896-6665.

Respectfully submitted,

Nisan A. Steinberg, Ph.D.
Registration No. 40,345

Sidley Austin Brown & Wood
555 West Fifth Street
Los Angeles, California 90013-1010
Telephone: (213) 896-6665
Facsimile: (213) 896-6600

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Intended deletions are marked with bold brackets to distinguish unbolded brackets properly found in the text of the specification.

In the Specification:

At page 2, lines 21-30, please delete the entire paragraph, and insert therefor the following paragraph:

--*PTTG* encodes a securin protein the expression of which causes cell transformation, induces the production of basic fibroblast growth factor (bFGF), is regulated in vitro and in vivo by estrogen, and inhibits chromatid separation. (Pei, L., and Melmed, S., *Isolation and characterization of a pituitary tumor transforming gene*, Mol. Endocrinol. 11:433-441 [1997]; Zhang, X., *et al.*, *Structure, expression, and function of human pituitary tumor-transform[rn]ing gene (PTTG)*, Mol. Endocrinol. 13:156-166 [1999a]; Heaney, A.P., *et al.*, *Early involvement of estrogen-induced pituitary tumor transforming gene and fibroblast growth factor expression in prolactinoma pathogenesis*, Nature Med. 5:1317-1321 [1999]; Zou, H., *et al.*, *Identification of a vertebrate sister-chromatid separation inhibitor involved in transformation and tu[rn]morigenesis*, Science 285:418-422 [1999]).--.

At page 5, lines 15-25, please delete the entire paragraph, and insert therefor the following paragraph:

--The sequence of events in angiogenesis leading to formation of new blood vessels from pre-existing vessels is highly regulated (Jain, RK *et al.*, *Quantitative angiogenesis assays: progress and problems*, Nat Med. 3:1203-1208 [1997]; Darland DC and D'Amore PA, [1999] *Blood vessel maturation: vascular development comes of age*[.], J Clin Invest. 103:157-158 [1999]), and involves dissolution of vessel basement membranes, and formation of new lumen and pericytes by vascular endothelial cells. During tumor-associated angiogenesis, sustained production of angiogenic factors by cancer cells, or indirect macrophage stimulation, causes disregulated immature vessel growth (Folkman, J. and Shing, Y., *Angiogenesis*, J Biol Chem. 267:10931-10934[1992]). A number of in vitro and in vivo assays have been useful for studying

angiogenesis (e.g., Jain, RK *et al.* [1997]; Auerbach, R. *et al., Assays for angiogenesis: a review*, Pharmacol Ther. 51:1-11 [1991]).--.

At page 9, lines 4-7, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 5 shows *PTTG* mRNA expression in normal adult human T-cells treated with mitogen anti-CD3 antibody. T-cells were isolated and stimulated with anti-CD3 antibody for 72 hours. *PTTG* mRNA [PTTG] was measured with northern blotting (middle panel) and percentage of cells in S or G2/M phase was determined by FACS.--.

At page 9, lines 8-11, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 6 shows *PTTG* mRNA expression in normal adult human T-cells treated with mitogen phytohemagglutinin (PHA). T-cells were isolated and stimulated with increasing concentrations of PHA for 72 hours. *PTTG* mRNA was measured with northern blotting (middle panel) and percentage of cells in S or G2/M phase was determined by FACS.--.

At page 9, lines 12-15, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 7 shows *IL-2* mRNA expression in normal adult human T cells treated with mitogen anti-CD3 antibody. T-cells were isolated and stimulated with anti-CD3 antibody for 72 hours. *IL-2* mRNA [PTTG](middle panel) was measured with northern blotting and percentage of cells in S or G2/M phase was determined by FACS.--.

At page 9, lines 16-18, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 8 shows cyclophilin mRNA expression in normal adult human T cells treated with mitogen anti-CD3 antibody. T cells were isolated and stimulated with anti-CD3 antibody for 48 hours. Cyclophiline mRNA (middle panel)[PTTG] was measured with northern blotting.--.

At page 9, lines 19-22, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 9 demonstrates *PTTG* mRNA expression and hydrocortisone. PHA (5 μg/mL)-stimulated normal adult human T cells were treated with hydrocortisone for 72 hours. *PTTG* mRNA was measured with northern blotting (middle panel) and percentage of cells in S or G2/M phase was determined by FACS.--.

At page 9, lines 23-25, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 10 shows *PTTG* mRNA expression and cyclosporin. PHA (5 μg/mL[l])-stimulated normal adult human T cells were treated with cyclosporin for 72 h. *PTTG* mRNA was measured with northern blotting (middle panel) and percentage of cells in S or G2/M phase was determined by FACS.--.

At page 10, lines 4-9, please delete the entire paragraph, and insert therefor the following paragraph:

--Figure 13 shows *PTTG* mRNA expression in human Jurkat T cell leukemia line. Jurkat T cells were treated as described below. (1) cells kept for 48 h in 1% FBS-supplemented culture medium; (2) cells after medium change for fresh 1% FBS-supplemented; (3) cells after medium change for 10% FBS-supplemented; (4) phytohemagglutinin (PHA; 1 μg/mL) + phorbol-12-meristate-13-acetate (PMA; 50 ng/mL) in 1% FBS; (5) (PHA + PMA) + cyclosporine A (1 μg/mL); (6) (PHA + PMA) + TGF-β1 (10 ng/mL). *PTTG* mRNA was measured with northern blotting (middle panel) and percentage of cells in S phase was determined by FACS.--.

At page 98, lines 13-24, please delete the entire paragraph, and insert therefor the following paragraph:

--Tube forming assay. Matrigel is useful for studying HUVEC attachment and differentiation. Since Matrigel itself induces HUVEC differential activity, we used GFR Matrigel[erial] to reduce the effect of growth factors from the Matrigel itself. As shown in Figure 22A, when HUVECs adhered on GFR Matrigel[eriel], they aligned with one another and formed tubes resembling a capillary plexus under the influence of differential activity in the CM. Quantitative analysis of HUVEC tube formation (Denekamp J., *Review article: angiogenesis, neovascular proliferation and vascular pathophysiology as targets for cancer therapy*, Br J Radiol. 66:181-196 [1993]) revealed that WT-hPTTG-CM enhanced HUVEC tube formation compared to that observed when HUVECs were incubated in CM derived from other cell lines (Figure 22B; $p<0.01$). The morphologic changes resembling capillary formation were suppressed by adding anti-bFGF antibody to each CM. Suppressive effects of anti-bFGF antibody of WT-hPTTG-CM, M-hPTTG-CM, C-CM and N-CM were, in the same order, 74%, 58%, 57%, and 62%.--.

At page 99, lines 1-13, please delete the entire paragraph, and insert therefor the following paragraph:

--CAM assay. PTTG-[]mediated angiogenic activity was also examined in vivo by CAM assay. Chick CAM provides an ideal microenvironment to induce new vessel development from pre-existing vessels. We observed that CM from WT-hPTTG-transfected cells induced a spoke-wheel like appearance on the CAM and this effect was more marked than that observed with CM derived from other cell lines. Vessel growth of CAM was tested in vivo using 9-day-old chick egg embryos. Sample-soaked collagen sponges were loaded on CAM and neovascularization of surrounding collagen sponges evaluated after 4 days incubation. As shown in Figure 23A, application of sponges presoaked in WT-hPTTG-CM induced a spoke-wheel like appearance which was more evident than CAM vessel formation after application of sponges immersed in the other CMs. The number of detectable blood vessels entering the collagen sponges were counted under stereomicroscopy (Figure 23B), and as predicted, all CM samples derived from both

transfected and non-transfected NIH-3T3 cells induced stronger angiogenic responses than did serum-free DMEM alone ($p<0.01$).--.

Between Figure 18 and Figure 20, please insert the following Figure 19 (next page):